REMARKS UNDER 37 CFR § 1.116

Formal Matters

Claims 1-11, 13, 14 and 16-20 are pending after entry of the amendments set forth herein.

Claims 1-11, 13, 14, 16 and 17 were examined. Claims 1-11, 13, 14, 16 and 17 were rejected.

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

Claims 16 are amended for clarity. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Accordingly, no new matter is added.

PTO 1449 form

Applicants respectfully request that the Examiner initial and return the PTO 1449 form submitted with the Information Disclosure Statement filed herewith in this application, thereby indicating that the references cited therein have been reviewed and made of record.

Specification

The specification is objected to as containing new matter. Specifically, the Office objects to paragraph [0028] of the substitute specification.

Since paragraph [0028] has been cancelled by amendment, this rejection is now moot.

Withdrawal of this rejection is respectfully requested.

Rejection under 35 USC § 112, second paragraph

Claims 14 and 16are rejected under 35 USC § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office Action asserts that the phrase "a protein processing precursor fibrous protein" is unclear.

In making the rejection, the Examiner suggested amending the claims to recite "a protein which processes a precursor fibrous protein".

The Applicants have amended claim 14 to recite "a protein which processes a precursor fibrous protein". In view of this amendment, and the fact that claim 16 does not appear to recite the phrase "a protein processing precursor fibrous protein", this rejection is believed to be moot.

Withdrawal of this rejection is respectfully requested.

Rejection under 35 USC § 102 – Kivirikki

Claims 1-4, 6, 8, 10-12, 14, 15 and 17 are rejected under 35 USC § 102(b) as being anticipated by Kivirikki (WO 97/38710). Specifically, the Office Action asserts that Kivirikki discloses a process for the production of a fibrous protein which anticipates the claims. The Applicants respectfully traverse this rejection.

As noted by the Examiner on at the top of page 6 of the Office Action, Kivirikki fails to disclose cells that are available in a transgenic plant, or methods that involve tropoelastin. Applicants also note that Kikrivikki fails to teach expression of a precursor protein and a precursor protein processing enzyme in *different* cells (claim 3).

In order to put Kivirikki in context, the Applicants point out the present invention is primarily concerned with a process for the production of mature fibrous protein by producing precursor fibrous proteins in plant cells and converting these precursors into mature fibrous protein by treatment with enzymes that process the precursor proteins. Example 2 clearly details a method for expressing tropocollagen in a plant cell with lysine oxidase, procollagen C proteinase and procollagen N proteinase. The proteinase enzymes are responsible for hydrolysing procollagen peptide bonds and lysine oxidase is responsible **for the formation of cross-links** between collagen fibrils, resulting in the production of mature collagen.

Firstly it should be noted that Kivirikki is overwhelmingly concerned with the expression of a procollagen or collagen in an insect or yeast cell. In respect of plant cells, there is no specific exemplification or disclosure provided on experimental procedures for expressing procollagen or a collagen along with a processing enzyme in a plant cell i.e. no enabling disclosure of all the features of the present invention together.

Likewise, although Kivirikki discusses a number of different protein-processing enzymes yet the document only discloses the use of one of these enzymes i.e. prolyl-4-hydroxylase, which is required for the hydroxylation of immature polypeptide chains to form the triple helix formation known as procollagen (see document, pages 30 onwards). The Examiner states that Kivirikki teaches methods in which lysine oxidase is expressed in the same host cell as the precursor protein or in a different host cell.

This is not the case. There is no specific teaching in the document of any method for expressing lysine oxidase with a precursor protein. The examples of Kivirikki are concerned with prolyl 4-hydroxylase only and therefore the skilled person is provided with a disclosure that would enable him to express procollagen, but not the mature form of collagen, in an insect or yeast cell only.

In addition, the Examiner believes that since Kivirikki teach the expression of a precursor protein that is procollagen, the fibrous protein produced is a collagen. In fact, only by expressing procollagen with the appropriate proteolytic enzyme would the formation of tropocollagen result. The mature, processed, cross-linked form of collagen would not be produced.

> "No doctrine of the patent law is better established than that a prior patent or other publication to be an anticipation must bear within its four corners adequate directions for the practice of the patent invalidated. If the earlier disclosure offers no more than a starting point for further experiments, if its teaching will sometimes succeed and sometimes fail, if it does not inform the art without more how to practice the new invention, it has not correspondingly enriched the store of common knowledge, and it is not an anticipation." Dewey & Almy Chemical Co. v. Mimex Co., 52 U.S.P.Q. 138, 142 (2d Cir. 1942) (Judge Learned Hand).[1]

The Applicants respectfully submit that Kivirikki fails to provide an enabling disclosure and, as such, Kivirikki cannot anticipate claims 1-4, 6, 8, 10-12, 14, 15 and 17. In view of the arguments set forth above, withdrawal of this rejection is respectfully requested.

Rejection under 35 USC § 102 – Daniell

Claims 1, 5, 7 and 9 are rejected under 35 USC § 102(e) as being anticipated by Daniell (US 6,004,782). Specifically, the Office Action asserts that Daniell discloses a process for the production of a fibrous protein which anticipates the claims. The Applicants respectfully traverse this rejection.

Like Kivirikki, Daniell is primarily concerned with a rather different invention than the present one - namely a particular (generally artificial) bioelastic polymer produced in inclusion bodies in procaryotes such as *E. coli* - indeed this is what the claims are limited to, and by inference what the disclosure enabled.

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[1] Judge Hand cited several cases in support of this analysis of the law: Seymour v. Osborne, 11 Wall. 516, 555, 20 L.Ed. 33; Tilghman v. Proctor, 102 U.S. 707, 711, 712, 26 L.Ed. 279; Eibel Process Co. v. Minnesota & Ontario Paper Co., 261 U.S. 45, 66, 43 S.Ct. 322, 67 L.Ed. 523; (Second Circuit) Westinghouse Air-Brake Co. v. Great Northern R. Co., 88 F. 258, 263; Hillard v. Fisther Book Typewriter Co., 159 F. 439, 441; United Chromium, Inc., v. International Silver Co., 60 F.2d 913, 917; H. K. Regar & Sons v. Scott & Williams, 63 F.2d 229, 231; (Third Circuit) Skelly Oil Co. v. Universal Oil Products Co., 31 F.2d 427, 431; American Safety Tably Co. v. Singer Sewing Machine Co., 95 F.2d 543, 549, 550; (Fourth Circuit) McKee v. Graton & Knight Co., 87 F.2d 262, 264; (Sixth Circuit) Morgan Construction Co. v. Wellman-Seaver-Morgan Co., 18 F.2d 395, 399; (Ninth Circuit) 4 F.2d 463, 465; (C.P.D.C.) In re Ek, 57 App.D.C. 203, 19 F.2d 677, 678; Becket v. Coe, 69 App.D.C. 51, 98 F.2d 332, 335; Ct. C. & P. App. In re Cramblet, 62 F.2d 358, 359.

Daniell does mention, in general, vectors and promoters for use in expressing nucleic acids in plant cells. However, the Applicants respectfully submit that Daniell does not disclose incubating a plant-expressed precursor fibrous protein with a protein for processing it, such that a fibrous protein is produced. For example, Examples 4-7 of Daniell detail the expression of bioelastic polypeptide in a host cell but the polypeptide is not expressed with a processing protein such that a mature protein is produced. In other words, although Daniell mention that the bioelastomer may or may not be cross-linked, it provides no detailed teaching of how the cross-linking may occur. There is no mention, for example, of the expression of a cross-linking enzyme, e.g., lysyl oxidase, in a cell, let alone a plant cell or how to incubate a precursor fibrous protein with this enzyme to produce the fibrous protein. In particular, Daniell fails to disclose expression of a cross-linking enzyme in the same plant cell to the bioelastic substrate.

Further, Applicants also note that Daniell, like Kivirikki, fails to teach expression of a precursor protein and a precursor protein and a precursor protein processing enzyme in *different* cells of a plant (claim 5).

In view of the above statements, the Applicants maintain that Daniell fails to disclose the combination of a precursor fibrous protein with a protein for processing it in a plant cell, fails to disclose a precursor fibrous protein and a protein for processing it in *different* cells, and does not provide an enabling disclosure. The Applicants respectfully submit that claims 1, 5, 7 and 9 are not anticipated by Daniell, and withdrawal of this rejection is respectfully requested.

Rejection under 35 USC § 103 – Kivirikki, in view of Zhang

Claims 1-17 are rejected under 35 USC § 103(a) as being obvious in view of Kivirikki, in view of Zhang (Plant Cell Reports, 1996, 16:174-179). Specifically, the Office Action asserts that Kivirikki's process for the production of a fibrous protein, combined with the methods taught by Zhang renders the claimed methods for producing transgenic plants that express fibrous precursor proteins obvious. The Applicants respectfully traverse this rejection.

In making the rejection, the Examiner states that Kivirikki do not teach methods in which the cells are available in a transgenic plant nor do they teach methods in which the precursor protein is a tropoelastin. However, Zhang does not meet Kivirikki's deficiencies. Furthermore, for a *prima facie* case of obviousness under 35 USC § 103, it is a requirement for the prior art to suggest the invention and to indicate a reasonable degree of success. As such, even if Zhang did meet Kivirikki's deficiencies, a *prima facie* case of obviousness cannot be made because the invention is not suggested by the

references, and a reasonable degree of success is not provided.

Firstly, the Applicants submit that the present invention is concerned with a process for the production of a fibrous *protein* - the expression of a precursor fibrous protein is one step in that process.

Kivirikki mentions that procollagen or collagen can be expressed in plant cells, but that this is not a preferred embodiment, nor is it enabled by the Kivirikki's specification. Zhang mentions that it is advantageous to produce proteins in plants because fermentation methods are expensive. However, Zhang go on to state that the yield obtained by producing proteins in plants using Zhangs methods was "low" and that "high expression must be achieved to produce protein based synthetic polymer gene products on an agricultural scale." In view of Zhang's statements about the unsuitability of his methods for producing synthetic polymer gene products, why would one of skill in the art want to produce a polymer using his methods? Since Zhang strongly "teaches away" from the invention, a skilled person would not combine these references with any reasonable expectation of success.

This point alone warrants withdrawal of this rejection.

Further, the suggestions made by Zhang in order to increase yield, e.g., 'additional genetic manipulation such as optimisation of codon usage or expression of the $(GVGVP)_{121}$ polymer gene in the chloroplast compartment' do not include the expression of fibrous protein precursors with processing enzymes. Therefore combining the teachings of Zhang with those of Kivirikki would not indicate any degree of success for a process of producing a fibrous protein in a plant cell.

In addition, Kivirikki only teach and exemplify the use of prolyl 4-hydroxylase. They do not teach methods in which lysyl oxidase is expressed in the same or different host cell as the precursor protein. Therefore there is no suggestion to incubate the tropoelastins produced in Zhang with any of the other processing proteins mentioned by Kivirikki to give cross-linked polymers for the commercial utilities discussed by Zhang. There is no indication in Zhang that cross-linked polymers are desirable or required. Since the methods taught in Zhang result in a low yield of polymers and that suggestions made in that document are directed towards improving yield, there is nothing in Zhang or Kivirikki to suggest that this could be achieved by incubating the synthetic polymers of Zhang with a protein processing enzyme other than prolyl 4-hydroxylse as taught by Kivirikki.

Finally, Applicants note that neither Zhang or Kivirikki disclose, teach, or suggest expression of a precursor protein and a precursor protein processing enzyme in *different* cells (claim 3) or expression of a precursor protein and a precursor protein and a precursor protein processing enzyme in *different* cells of a plant (claim 5). Since these claim limitations are not taught or suggested by the disclosures of Zhang or Kivirikki, the cited references cannot render the subject matters of those claims obvious.

In view of the above discussion, the Applicants respectfully submit that the present invention is not obvious over Kivirikki in view of Zhang. Withdrawal of this rejection of claims 1-17 is respectfully requested.

Conclusion

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number MEWE-019.

Respectfully submitted,
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